Table I. Selected ^{1}H NMR Data for Cycloadducts[16]

	compound			
	10n	**10x**	**13n**	**13x**
R	Me	Me	$(CH_2)_2Me_3Si$	$(CH_2)_2Me_3Si$
R'	H	H	Ph	Ph
H_a	7.26	7.35	7.17	7.30
H_b	5.95	6.20	6.01	6.25
H_c	5.79	5.84	5.78	5.84
H_d	4.77	4.33	4.81	4.39
H_e	4.00	4.12	4.17	4.27
J_{ae}	6.75	6.1	6.85	6.2
J_{cd}	4.7	2.0	4.7	2.2
J_{ac}	2.4	1.75	2.3	~1.0

In order to test the generality of this novel cycloaddition and to produce compounds more amenable for conversion to the ivermectin bottom half, we prepared two analogous components for additional cycloadditions. A slight modification of the literature route[7] allowed the preparation of 3,4-bis(benzyloxy)furan (**6b**) from diglycolic acid in five steps. Conversion of coumalic acid to its acid chloride ($SOCl_2/\Delta/6$ h/80%) followed by reaction with 2-(trimethylsilyl)ethanol (pyr/Et_2O–THF/–5 to 25 °C/3 h/65%) gave the silylethyl coumalate **1b**. Cycloaddition of **1b** with **6b** as before ($MeOH/\Delta/3$ h) gave a 1:1 mixture of **13n/13x** in 38%
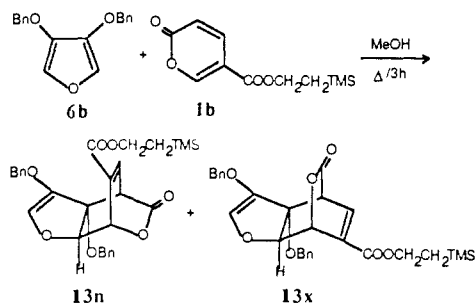

yield with approximately 20% of a 2:1 furan/pyrone adduct being formed for which the structure **14** has been assigned.[13] However,

14
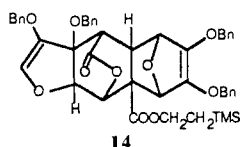
modification of the reaction conditions as follows permitted us to overcome this obstacle. Refluxing a methanol solution containing 10 equiv of **1b** and 1 equiv of **6b** for 3 h followed by silica gel chromatography afforded an 86% yield of **13n** and **13x** in a ratio of 53:47 with only a trace of **14** being produced. In addition this simple chromatography returned 86% of the unreacted coumalate **1b** in pure form for use in further cycloadditions. The structures of the endo and exo adducts **13n/13x** were assigned by the close similarity of their ^{1}H NMR spectra to those of **10n** and **10x**, respectively, especially the coupling constants of H_c and H_e (Table I).

Further attempted cycloadditions of 5-substituted pyrone derivatives highlight the necessity that C-5 not bear an electron-donating group, even a methyl group. For example, 5-methylpyrone and its 2-substituted derivatives **15a–d**[14] were all prepared

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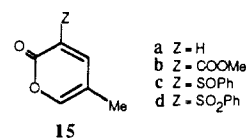
but did not add to **1a** or **1b** under normal conditions (MeOH or $PhCH_3$ at reflux).[15] The use of catalytic Lewis acids in these reactions gave back the coumalates but decomposed the electron-rich furans.

In summary we have demonstrated that two non-benzenoid aromatic systems can lose aromaticity in a single thermal cycloaddition under mild conditions. Further we have shown that a 3,4-dialkoxyfuran prefers to react as a dienophile rather than a diene with alkyl coumalates in a completely regioselective manner. Finally the conversion of some of these intermediates, e.g., **13n**, into compounds, e.g., **9**, which might serve as components for the bottom half of ivermectin is under way and will be reported in due course.

(14) 5-Methylpyrone (**15a**) was prepared by a modification of the known route: Takeuchi, Y.; Makino, Y.; Maruyama, K.; Yoshii, E. *Heterocycles* **1980**, *14*, 163–168. The other pyrones, **15b–d**, were all prepared by new routes which will be described in detail elsewhere.

(15) At temperatures much higher than refluxing benzene, elimination of carbon dioxide and a mole of alcohol occurs to produce the alkoxy-substituted benzoate.[4a,c,e] Therefore, the use of higher temperatures was precluded.

(16) Chemical shift data is given in parts per million downfield from internal tetramethylsilane and coupling constants are in hertz. The spectra were recorded at 500 MHz. Other resonances in the spectra are as follows: **10n**, 3.82 (3 H, s), 3.57 (3 H, s), 3.35 (3 H, s); **10x**, 3.83 (3 H, s), 3.61 (3 H, s), 3.24 (3 H, s); **13n**, 7.40–7.26 (10 H, m), 4.69 (2 H, AB q, $J = 11.2$ Hz), 4.65 (2 H, s), 4.30 (2 H, m), 1.05 (2 H, m), 0.06 (9 H, s); **13x**, 7.40–7.24 (10 H, m), 4.74 (2 H, s), 4.55 (2 H, d, $J = 11.5$ Hz), 4.46 (2 H, d, $J = 11.5$ Hz), 4.31 (2 H, m), 1.05 (2 H, m), 0.06 (9 H, s).

Additivity in Complex CD Curves of Multichromophoric Systems

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Interaction of the transition moments of two or more chromophores within a chiral molecule constitutes a coupled oscillator, which gives rise to a split CD curve. The closer the λ_{max} of interacting chromophores, the more efficient the coupling, yet a split CD is observed even when the λ_{max} values differ by as much as 80 nm.[1,2]

In hexopyranoside[3] and trichothecene[4] tri- and tetrabenzoates, and more recently pyranoside benzylates,[5] the amplitudes of split

(1) (a) Harada, N.; Nakanishi, K. *Acc. Chem. Res.* **1972**, *5*, 257. (b) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy—Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983; p 550ff. (c) Harada, N.; Iwabuchi, J.; Yokota, Y.; Uda, H.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 5590.

(2) Nakanishi, K.; Kuroyanagi, M.; Nambu, H.; Oltz, E. M.; Takeda, R.; Verdine, G. L.; Zask, A. *Pure Appl. Chem.* **1984**, *56*, 1031.

(3) Lui, H. W.; Nakanishi, K. *J. Am. Chem. Soc.* **1982**, *104*, 1178.

(4) Oltz, E. M.; Nakanishi, K.; Yagen, B.; Corley, D. G.; Rottinghaus, G. E.; Tempesta, M. S. *Tetrahedron* **1986**, *42*, 2615.

(5) Takeda, R.; Nakanishi, K., unpublished results.
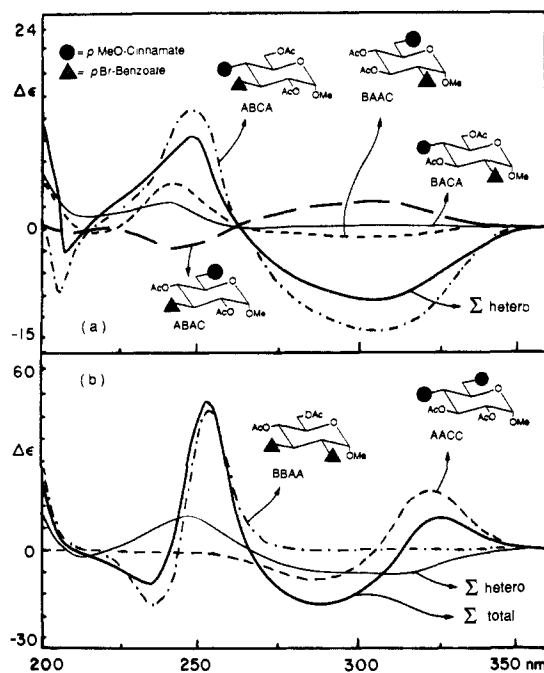
(13) Compound **14** is a mixture of stereoisomers, presumably formed by initial reaction in the desired sense to give **13n** and **13x**, followed by Diels–Alder addition of the electron-rich furan to the strained acrylate unit of the product.

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Communications to the Editor

Figure 1. Calculation of the CD curve of methyl α-D-glucopyranoside 2,3-dibromobenzoate 4,6-dimethoxycinnamate (BBCC). (a) The CD curves of the four contributing hetero interactions. The sum of these four hetero interactions is shown as ∑(hetero). (b) Summation of the two homo interactions BBAA and AACC and the summed hetero interactions (∑(hetero), Figure 1a.) give the empirically calculated CD spectrum (∑(total)) of the 2,3-dibenzoate 4,6-dicinnamate.

Figure 2. Comparison of calculated and observed spectra: (a) the 2,3-dibenzoate 4,6-dicinnamate (BBCC calculated in Figure 1.) and 2,6-dibenzoate 3,4-dicinnamate (BCCB); (b) 4-cinnamate 2,3,6-tribenzoate (BBCB) and 4-acetate 3-benzoate 2,6-dicinnamate (CBAC).

CD curves (A values) can be approximated by the sum of constituent dichromophoric interactions. This additivity relation was found for nearly degenerate benzoate (230 nm)/enone (244 nm) interactions in complex ecdysteroids as well.[6] However, full spectral summation of contributing interactions must replace A value addition when nondegenerate interactions are involved. We herein report the general validity of additivity by demonstrating that complex CD spectra of 17 methyl α-glucopyranoside p-bromobenzoate p-methoxycinnamates can be fully calculated by spectral summation of all degenerate and nondegenerate constituent interactions.

In connection with attempts to develop an exciton chirality microanalysis of glycosidic linkages,[2] it has now been shown that addition of a red-shifted chromophore to hexopyranoside p-bromobenzoates (λ_{max} 244 nm) results in complex and unique CD spectra. The p-methoxycinnamate chromophore (λ_{max} 311 nm, ε 24000) was chosen: benzoate/benzoate (B/B) and cinnamate/cinnamate (C/C) degenerate ("homo") interactions are well separated, yet strong benzoate/cinnamate (B/C) nondegenerate "hetero" interactions are still observed. Such "bichromophoric" systems thus have up to three types of partially overlapping interactions, i.e., B/B, C/C, and B/C.

To determine the contribution of every possible dichromophoric interaction, all 24 possible methyl α-D-glucopyranosides containing two chromophoric esters were prepared (the free hydroxyls were converted to "nonchromophoric" acetates to best simulate ring conformation in the tetraesters studied). The six dibenzoate interactions resulted in split CD's with extrema at 236/253 nm, while the six dicinnamate diacetates showed typical splitting with extrema around 287/322 nm. The 12 monobenzoate monocinnamate diacetates showed hetero split CD interactions (as in Figure 1a) with extrema around 246/303 nm and broad shoulders around 285 and 310 nm.

These 24 derivatives were prepared via combinations of partial acetylations, benzoylations, and cinnamylations, as were 17 tri- and tetrachromophoric test cases. For example, partial p-meth-
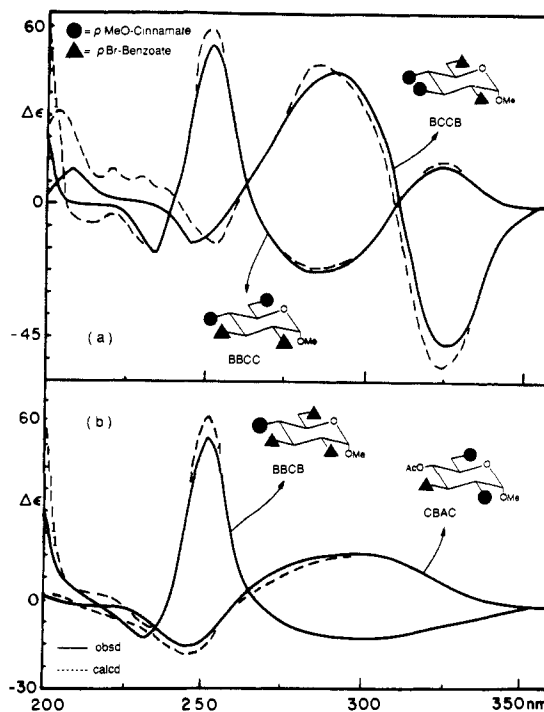
oxycinnamylation (acid chloride[7]/pyridine/DMAP, 60 °C) of the parent glucoside yielded three mono products (2-, 3- and 6-), five dicinnamates (all except 3,4-), and two tricinnamates (2,3,6- and 2,4,6-). Each of these intermediates could then be acetylated and/or benzoylated. The 17 multichromphoric additivity test cases can be divided into five classes: monocinnamate di- and tribenzoates, monobenzoate di- and tricinnamates, and dibenzoate dicinnamates. The CD spectra of all 41 HPLC-purified derivatives were normalized to 1.0 × 10⁻⁵ M from the UV-determined concentrations.[8]

Additivity studies involved summation of the appropriate three or six dichromophore spectra which correspond respectively to the contributing interactions in a tri- or tetrachromophoric case. For example, the spectra of the four hetero interactions contributing to the spectrum of the 2,3-dibenzoate 4,6-dicinnamate "BBCC" are shown in Figure 1a (derivitization of the four positions is represented in the order 2, 3, 4, 6 by A = acetate, B = p-bromobenzoate, C = p-methoxycinnamate). The sum of these four (∑(hetero)) is then added to the two appropriate homo interactions BBAA and AACC (Figure 1b) to give the sum total (∑(total)) of all contributing interactions, the empirically calculated CD spectrum of methyl α-D-glucopyranoside 2,3-bis(p-bromobenzoate) 4,6-bis(p-methoxycinnamate).

Calculated and observed spectra for this and another dibenzoate dicinnamate BCCB involving B/C, B/B, and C/C interactions are shown in Figure 2a. All six possible derivatives in this most complex dibenzoate/dicinnamate class were prepared; calculated spectra show excellent agreement with observed spectra for these as well as other classes of multichromophoric derivatives (Figure 2b.). The CD curves suggest the type, magnitude and sign of the interactions involved. The spectrum of the 4-cinnamate 2,3,6-tribenzoate (BBCB) is clearly dominated by the homo benzoate coupling, while in the case of CBAC, hetero coupling accounts

(6) Stonard, R. J.; Trainor, D. A.; Nakatani, M.; Nakanishi, K. J. Am. Chem. Soc. **1983**, 105, 130.

(7) Andrews, E. R.; Van Campen, M. G.; Schumann, E. L. J. Am. Chem. Soc. **1953**, 75, 4003.

(8) Acetonitrile rather than methanol was used as solvent in order to avoid ester exchange during CD/UV measurements: Golik, J.; Liu, H. W.; Dinovi, M.; Furukawa, J.; Nakanishi, K. Carbhydr. Res. **1983**, 118, 135. CD spectra were recorded on a Jasco J-500A spectropolarimeter. Spectral normalization and summation were performed on an IBM-PC operating with Jasco software. No appreciable concentration dependence was observed.

for most of the splitting. Excellent agreement is also observed in the galactose series.

The accuracy of these additive calculations indicates the general validity of the additivity principle and thus justifies the use of a simple retro-additive approach to the interpretation of complex CD spectra. Application of selective bichromophoric derivatization to complex stereochemical problems can provide for interpretable information-rich CD spectra of nanomolar quantities. Such an approach is currently being applied to oligosaccharide micro-analysis, wherein the free hydroxyls are derivatized with one type of chromophore and the linkage positions are tagged with a second chromophore. Resulting subunits are then fully characterized by UV (to determine chromophoric ratios) and CD measurements.

Determination of Dipole–Dipole Couplings in Oriented n-Hexane by Two-Dimensional NMR

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NMR spectra of molecules partially oriented in liquid crystals contain information about the anisotropic dipole–dipole interactions of the spins. It is of interest to recover the intramolecular dipolar coupling constants D_{ij} between each pair of spins since D_{ij} is proportional to $\langle r_{ij}^{-3} \rangle$ and quantitatively describes the molecular structure and the motions affecting the structure.[1] However, in conventional NMR spectroscopy the number of detectable transitions becomes intractably large as the number of active spins increases, and the individual lines may no longer be resolvable. In n-hexane, which is the molecule of interest here, the number of distinct transitions, even taking into account the symmetry of the molecule, can be as large as 60 000, concealing the 16 unique dipolar couplings between protons.

Several techniques have been proposed to overcome this problem. One useful approach is selective isotopic substitution, e.g., selective positioning of protons in otherwise deuterated molecules and measurement of the NMR spectrum under conditions of deuterium decoupling.[2,3] This allows an arbitrary reduction of the number of active spins but requires demanding synthetic effort. Another possible solution is the observation of high-order multiple-quantum spectra in order to reduce the redundant information in single-quantum NMR spectra.[4]

We give here a preliminary report of an alternative method to analyze spectra and determine structures of molecules dissolved in liquid crystals. The basic idea is the use of randomly deuterated samples (a synthetically facile undertaking) which contain a mixture of all possible isotopomers of a molecule. This approach has been used before in the analysis of some cyclic compounds[3,5,6] in nematic liquid crystals. A highly deuterated sample will contain mostly isotopomers with just a few protons. Thus, the task of
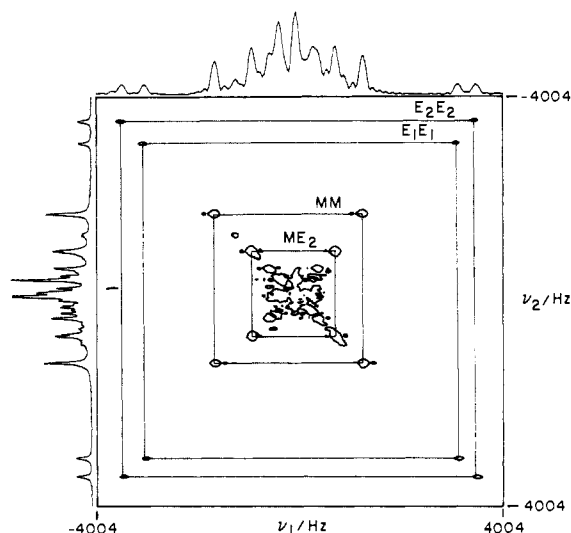

Figure 1. Two-quantum filtered COSY-type spectrum of 81% randomly deuterated n-hexane, 23 mol % in EK 11650, taken with the pulse sequence described in the text. Deuterium-decoupled FIDs, 128 × 1024 points, were collected on a 360-MHz spectrometer (nonquadrature in t_1) with a spectral width of 16 667 Hz in both dimensions and a recycle delay of 5 s. For each t_1 point, 200 FIDs were accumulated while the double-quantum mixing time τ_1 was incremented from 0 to 9800 μs in 200-μs steps after every fourth FID. For τ_2, 4 ms was used. The data set was zero-filled to 512 × 2048 points prior to Fourier transformation. The square patterns which give the dipole coupling constants are illustrated for four of the 16 proton pairs.

Table I. List of Dipole Coupling Constants Obtained for the Eight AB and Eight A_2 Coupling Patterns

sites	$D_{ij}{}^{a,c}$	$D_{ij}{}^{b,c}$	sites	$D_{ij}{}^{a,c}$	$D_{ij}{}^{b,c}$
E_1E_1	3974	3968	E_1E_2	186	183
E_1E_1	713	706	E_1E_2	81	81
E_1E_1	609	612	MM	1876	1862
E_2E_2	4487	4482	MM	206	203
E_2E_2	190	189	ME_1	386	382
E_2E_2	43	48	ME_1	322	314
E_1E_2	1616	1626	ME_2	1034	1041
E_1E_2	1086	1106	ME_2	598	591

^{a} The COSY-type experiment. ^{b} The INADEQUATE-type experiment. ^{c} The dipole coupling constants D_{ij} are defined by the equation $\mathcal{H}_D = \sum_{i<j} D_{ij}(3I_{zi}I_{zj} - I_iI_j)/2$.

interpreting one complex spectrum is reduced to one of analyzing a large number of simple but overlapping spectra. The crucial point is the ability to recognize the individual signals which derive from the same spin system (arise from one isotopomer). This can be achieved by the combined application of two-dimensional NMR[7] and multiple-quantum NMR[8,9] techniques as is shown below for the case of n-hexane.

An 81% randomly deuterated sample of n-hexane was synthesized by exchange of n-hexane in the gaseous phase with D_2 over Pd on charcoal at 190 °C. It was determined by mass spectroscopy to have a statistical distribution of isotopomers. Most molecules have between 0 to 5 protons on the chain. Figure 1 shows a two-quantum filtered[10,11] COSY-type spectrum of the mixture, taken with the pulse sequence

$$(\pi/2)_\phi - t_1 - (\pi/2)_\phi - \tau_1/2 - \pi_x - \tau_1/2 - (\pi/2)_x - \tau_2/2 - \pi_x - \tau_2/2\text{-sample}$$

The phase ϕ is incremented in 90° steps, alternating the receiver

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(1) Vericini, C. A.; Longeri, M. In *Nuclear Magnetic Resonance of Liquid Crystals*; Emsley, J. W., Ed.; D. Reidel: Dordrecht, 1985; Chapter 6. Diehl, P. *Ibid.*; Chapter 7.

(2) Charvolin, J.; Deloche, B. In *Molecular Physic of Liquid Crystals*; Luckhurst, G. R., Gray, G. W. Eds.; Academic: London, 1979, Chapter 15.

(3) Poupko, R.; Luz, Z.; Zimmerman, H. *J. Am. Chem. Soc.* **1982**, *104*, 5307–5314.

(4) Drobny, G.; Weitekamp, D. P.; Pines, A., submitted for publication in *J. Chem. Phys.*

(5) Hewitt, R. C.; Meiboom, S.; Snyder, L. C. *J. Chem. Phys.* **1973**, *58*, 5089–5095.

(6) Luz, Z.; Meiboom, S. *J. Chem. Phys.* **1973**, *59*, 1077–1091.

(7) Aue, W. P.; Bartholdi, E.; Ernst, R. R. *J. Chem. Phys.* **1976**, *64*, 2229–2246.

(8) Munowitz, M.; Pines, A., submitted for publication in *Adv. Chem. Phys.*

(9) Bodenhausen, G. *Prog. Nucl. Magn. Reson. Spectrosc.* **1981**, *14*, 137–173.

(10) Shaka, A. J.; Freeman, R. *J. Magn. Reson.* **1983**, *51*, 169–173.

(11) Sorensen, O. W.; Levitt, M. H.; Ernst, R. R. *J. Magn. Reson.* **1983**, *55*, 104–113.